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Claims

1. A method to identify a desired region of a target nucleic acid to be targeted for observation, which method comprises

contacting said nucleic acid with first and second identification probes, which probes comprise first and second oligomers specific for the upstream and downstream sequences bracketing said region respectively,

wherein said first oligomer is coupled to a first particulate label and said second oligomer is coupled to a second particulate label and wherein said particulate labels are observable by microscopy.

2. The method of claim 1, wherein said first and second particulate labels comprise fluorophores.

3. The method of claim 1, wherein said first and second labels are different.

4. The method of claim 1, wherein said first and second oligomers are peptide nucleic acids.

5. The method of claim 1, wherein said target nucleic acid is single-stranded and said first and second oligomers are complementary to the upstream and downstream sequences bracketing said region.

6. The method of claim 1, wherein said target nucleic acid is double-stranded and said first and second oligomers form triplexes with said upstream and downstream sequences bracketing said region.

7. The method of claim 1, which is performed simultaneously on a multiplicity of target nucleic acids using a multiplicity of identification probes having particulate labels of differing hues coupled to oligomers comprising sequences complementary to a multiplicity of said upstream and downstream sequences bracketing a multiplicity of such regions.

8. A method to detect the presence of a target nucleic acid of known sequence, which method comprises

contacting said nucleic acid with at least first and second identification probes, which probes comprise first and second oligomers specific for proximal nucleotide sequences of said nucleic acid,

wherein said first oligomer is coupled to a first particulate label and said second oligomer is coupled to a second particulate label and wherein said particulate labels are observable by microscopy.

9. The method of claim 8, wherein said first and second particulate labels comprise fluorophores.

10. The method of claim 8, wherein said first and second labels are the same.

11. The method of claim 8, wherein said first and second oligomers are peptide nucleic acids.

12. The method of claim 8, wherein said target nucleic acid is single-stranded and said first and second oligomers are complementary to the upstream and downstream sequences bracketing said region.

13. The method of claim 8, wherein said target nucleic acid is double-stranded and said first and second oligomers form triplexes with said upstream and downstream sequences bracketing said region.

14. The method of claim 8, which is performed simultaneously on a multiplicity of target nucleic acids, using a multiplicity of identification probes having particulate labels of differing hues for each known sequence targeted coupled to oligomers with different specificities according to the sequences targeted.

15. The method of claim 8, wherein said target nucleic acid of known sequence is derived from an organism.

16. The method of claim 15, wherein the organism is an infectious agent.

17. The method of claim 15, wherein the organism is a human subject.

18. A composition which comprises a target nucleic acid, said nucleic acid comprising a region bracketed by sequences formed by binding to a first oligomer and a second oligomer, said first oligomer coupled to a first particulate label and the second oligomer coupled to a second particulate label wherein said first and second particulate labels are observable by microscopy.

19. The composition of claim 18, wherein said first and second oligomers are peptide nucleic acids.

20. The composition of claim 18, wherein said target nucleic acid is single-stranded and said region is bracketed by double-stranded sequences formed by hybridizing to said first and second oligomers.

21. The composition of claim 18, wherein said target nucleic acid is double-stranded and comprises a region bracketed by triplex sequences formed by triplexing to said first and second oligomers.

22. The composition of claim 18, wherein said region comprises repetitive elements.

23. The composition of claim 22, wherein said repetitive elements are coupled to signal-generating moieties.

24. The composition of claim 20, wherein said target nucleic acid includes, associated with said bracketed region, at least one assay probe.

25. The composition of claim 24, wherein said assay probe comprises a terminator linked through an offsetting moiety to a fluorophore or to means for coupling a fluorophore.

26. The composition of claim 25, wherein said means for coupling a fluorophore comprises a member of a specific binding pair.

27. The composition of claim 26, wherein said assay probe is coupled to a detection probe, which comprises a fluorophore coupled to the complementary member of the specific binding pair.

28. A method to assess the length of a target nucleic acid segment that is composed of a variable number of repeated sequences which method comprises

coupling a first identification probe comprising a first particulate label coupled to a first oligomer specific for a sequence upstream of said segment and optionally a second identification probe comprising a second particulate label coupled to a second oligomer specific for a sequence downstream of said segment wherein said first and second labels are observable by microscopy;

coupling each repeated sequence in said segment to a signal generating moiety of predetermined intensity; and

observing the total intensity of said signal generating moiety coupled to said first and second particulate label.

29. The method of claim 28, wherein said observing is by means of a wide field microscope.

30. The method of claim 28, wherein said first and second particulate labels are of different hues.

31. The method of claim 28, which is performed simultaneously on a multiplicity of target nucleic acids using a multiplicity of identification probes having particulate labels of differing hues coupled to oligomers with different specificities according to the sequences upstream and downstream of the target nucleic acid segments.

32. The method of claim 28, wherein said target nucleic acid segment is single-stranded and said first and second oligomers are complementary thereto.

33. The method of claim 28, wherein said target nucleic acid segment is double-stranded and said first and second oligomers form triplexes therewith.

34. A method to detect a single nucleotide polymorphism (SNP) at a base that is included in a restriction site haploid, which method comprises

reacting a single-stranded nucleic acid target to be tested for the presence of said SNP with a first identification probe which comprises a first oligonucleotide coupled to a first particulate label, which first oligonucleotide contains a complementary restriction site haploid and is further complementary to the portion of the test nucleic acid that contains said base such that said complementary restriction site haploids together generate a restriction site;

reacting said test nucleic acid with a second identification probe which comprises a second oligonucleotide coupled to a second particulate label, which second nucleotide is complementary to a portion of the nucleic acid target proximal to the restriction site haploid

whereby double-stranded nucleic acid containing a restriction site is obtained when the restriction site haploid in said first oligonucleotide is complementary to a restriction site haploid in the test nucleic acid target;

treating said double-stranded nucleic acid with a restriction enzyme which cleaves at said restriction site; and

observing the association or dissociation of said first and second particulate label,

whereby continued association of said first and second particulate labels indicates the absence of the complement to said first oligomer restriction site haploid and dissociation of said first and second particulate label indicates the presence of the complement to said first oligomer restriction site haploid.

35. The method of claim 34, wherein said first and second particulate labels are of different hues.

36. The method of claim 35, wherein said observing is by means of a wide field microscope.

37. The method of claim 35, which is performed simultaneously on a multiplicity of single-stranded DNA targets and wherein said method comprises contacting said multiplicity of targets with a corresponding number of first and second identification probes having particulate

labels of different hues such that the first and second identification probes for each target comprises a particulate label of different hue from that of the first and second identification probes of the remaining targets in said multiplicity.

38. A method to detect a single nucleotide polymorphism (SNP) which method comprises

providing a reaction mixture that has been prepared by reacting a single-stranded nucleic acid target to be tested with a first identification probe comprising a first oligomer, coupled to a first particulate label, which first oligomer is complementary to said target and has a 3′ terminus which is complementary to the nucleotide immediately upstream of a base to be interrogated and by reacting said target with an assay probe which probe comprises a terminator complementary to one embodiment of said base, coupled to a fluorophore or a means to attach said fluorophore through a linker which offsets said fluorophore or a means to attach said fluorophore; and optionally, by reacting the target nucleic acid with a second identification probe comprising a second oligomer coupled to a second particulate label which is complementary to the target nucleic acid proximal to the base to be interrogated; and

treating said reaction mixture with a polymerase

whereby, if said embodiment of the interrogated base is present, the assay probe is incorporated; and

if necessary, attaching a fluorophore to said means to attach a fluorophore; and

observing the association of said fluorophore with said first particulate label and optionally with said second particulate label, whereby the association of the fluorophore with said label(s) indicates the presence of said embodiment of the interrogated base, and the absence of said association indicates the absence of said embodiment.

39. The method of claim 38, wherein said terminator is a dideoxynucleotide complementary to the embodiment of said base, said means to attach a fluorophore comprises a member of a specific binding pair.

40. The method of claim 39, wherein the members of said specific binding pair are nucleotide sequences of at least four nucleotides.

41. The method of claim 39, wherein said specific binding pair is biotin/avidin, antigen/antibody or receptor/ligand.

42. The method of claim 38, which further comprises coupling said means to attach a fluorophore to a detection probe comprising said fluorophore.

43. The method of claim 42, wherein said detection probe comprises said fluorophore coupled to the complementary member of the specific binding pair.

44. The method of claim 38, wherein said observing is by means of a wide field microscope.

45. A method to detect a SNP in a single-stranded nucleotide target, which method comprises

identifying the locus of a base to be interrogated for the presence or absence of a referent base by hybridizing a first identification probe comprising a first oligomer coupled to a particulate label and optionally a second identification probe comprising a second oligomer coupled to a second particulate label at the border(s) of said locus,

treating said hybridized target with a 5-mer assay probe which is completely complementary to said locus when one embodiment of said base is present; and

observing the presence or absence of said assay probe in association with said labels,

whereby the presence of said assay probe associated with said labels indicates the presence of the embodiment of the base and the absence of said assay probe associated with said labels indicates the absence of said embodiment of the base.

46. The method of claim 45 wherein said observing is by means of a wide field microscope.

47. The method of claim 45, wherein said 5-mer is a peptide nucleic acid.